For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack

Belumosudil Tablets 200mg

REZUROCK®

1. Generic Name

Belumosudil Tablets 200mg

2. Qualitative and quantitative composition

Each film-coated tablet contains 200 mg belumosudil (equivalent to 242.5 mg belumosudil mesylate).

Excipients (per 200 mg tablet):

Tablet core: microcrystalline cellulose (219 mg), hypromellose (25 mg), croscarmellose sodium (10 mg), colloidal silicon dioxide (1 mg), and magnesium stearate (2.5 mg).

Coating Composition: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide and yellow iron oxide.

3. Dosage form and strength

Each 200 mg tablet is a pale-yellow film-coated oblong tablet.

4. Clinical particulars

4.1 Therapeutic indication

Belumosudil is indicated for the treatment of patients 12 years and older with chronic graft-versus-host disease (chronic GvHD) after failure of at least two prior lines of systemic therapy.

4.2 Posology and method of administration

General

The recommended dose of belumosudil is 200 mg given orally once daily.

Dose Modifications

The recommended belumosudil dosage modifications in case of adverse reactions are provided below.

Table 1 - Recommended Dosage Modifications for Belumosudil for Adverse Reactions

Adverse Reaction	Severity*	Belumosudil Dose Modification
Hepatotoxicity (see Section Adverse Reactions)	Grade 3 ALT or AST (>5 to 20 × ULN) or Grade 2 bilirubin (>1.5 to 3 × ULN)	Hold belumosudil until recovery to ≤ Grade 1, then resume belumosudil recommended dose.
	Grade 4 ALT or AST (>20 × ULN) or Grade ≥3 bilirubin (>3 × ULN)	Permanently discontinue belumosudil.
Other adverse reactions (see Section Adverse Reactions)	Grade 3	Hold belumosudil until recovery to ≤ Grade 1, then resume belumosudil at the recommended dose level.
	Grade 4	Permanently discontinue belumosudil.

*Based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03

Dosage Modification Due to Drug Interactions

Strong CYP3A Inducers

Increase the dosage of belumosudil to 200 mg twice daily when co-administered with strong CYP3A inducers (see Section Interactions).

Proton Pump Inhibitors

Increase the dosage of belumosudil to 200 mg twice daily when co-administered with proton pump inhibitors (see Section Interactions).

SPECIAL POPULATIONS

Pediatric patients

The safety and effectiveness of belumosudil tablets in pediatric patients aged less than 12 years have not been established.

Elderly patients

No dose adjustment is recommended over the age of 65 years. Of the 186 patients with chronic GvHD in clinical studies of belumosudil, 25.8% were 65 years and older. No overall differences in safety or effectiveness of belumosudil were observed between these patients and younger patients (see Section Pharmacokinetic properties).

Hepatic impairment

No dose adjustment is recommended when administering belumosudil to patients with mild or moderate hepatic impairment (Child-Pugh A and B). The safety and efficacy of belumosudil in severe (Child-Pugh C) hepatic impairment has not been evaluated. For patients with pre-existing severe hepatic impairment (Child-Pugh C), consider the risks and potential benefits before initiating treatment with belumosudil.

Monitor patients frequently for adverse reactions (see Section Pharmacokinetic properties).

Renal impairment
No dose adjustment is recommended in patients with mild or moderate renal impairment. The effect of severe renal impairment has not been evaluated (see Section Pharmacokinetic properties).

Administration

Belumosudil tablets should be taken orally once daily at approximately the same time each day with a meal.

If the patient misses a dose of belumosudil, instruct the patient not to take extra doses to make up the missed dose.

4.3 Contraindications

Belumosudil is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation.

4.4 Special warnings and precautions for use

Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, belumosudil can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of belumosudil to pregnant rats and rabbits during the period of organogenesis caused adverse developmental outcomes including embryo-fetal mortality and malformations at maternal exposures (AUC) less than those in patients at the recommended dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil (see Section Pregnancy and Non clinical properties).

4.5 Drugs interactions

Effect of other drugs on belumosudil

Strong CYP3A4 Inducers

Coadministration of belumosudil with strong CYP3A inducers decreases belumosudil exposure, (see Section Pharmacological properties) which may reduce the efficacy of belumosudil. Increase the dosage of belumosudil when co-administered with strong CYP3A inducers (see Section Posology and Method of administration).

Proton Pump Inhibitors

Coadministration of belumosudil with proton pump inhibitors decreases belumosudil exposure, (see Section Pharmacological properties) which may reduce the efficacy of belumosudil. Increase the dosage of belumosudil when co-administered with proton pump inhibitors (see Section Posology and Method of administration).

Effect of belumosudil on other drugs

OATP1B1/BCRP substrates:

Coadministration of belumosudil with drugs transported by OATP1B1 and BCRP can lead to an increase in exposure of these concomitant drugs (e.g. rosuvastatin) which may increase the risk of these substrate-related toxicities. Consider switching to a drug less sensitive to OATP1B1 and BCRP inhibition when possible. If used together the dose of rosuvastatin should not exceed 5 mg once daily. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 and BCRP (see Section Pharmacokinetic properties).

Drug-Food Interactions

In healthy subjects, the administration of a single 200 mg dose of belumosudil with a high-fat and high-calorie meal (800 to 1,000 calories with approximately 50% of total caloric content of the meal from fat) increased C_{max} to 2.2 times that following fasted administration and AUC to 2 times that following fasted administration. Median T_{max} was delayed 0.5 hours.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy
Verify the pregnancy status of females of reproductive potential prior to initiating treatment with belumosudil.

Based on findings from animal studies and the mechanism of action, (see Section Reproductive and Developmental Toxicity) belumosudil can cause fetal harm when administered to pregnant women. There are no available data on belumosudil use in pregnant women. No conclusions can be drawn regarding whether or not belumosudil is safe for use during pregnancy. The use of belumosudil in pregnant women is not recommended.

Contraception

Females
Advise females of reproductive potential to use effective contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males
Advise male patients with female partners of reproductive potential to use effective contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil.

Lactation
No human or animal data are available to assess the impact of belumosudil on milk production, its presence in breast milk, or its effects on the breastfed infant. No conclusions can be drawn regarding whether belumosudil is safe for use during breastfeeding. Breastfeeding is not recommended during treatment with belumosudil and for at least one week after the last dose.

Fertility
No human data are available to determine potential effects of belumosudil on fertility in females and males.

Based on findings from rats, belumosudil may impair female fertility. Based on findings from rats and dogs,

belumosudil may impair male fertility. The effect on male and female fertility is reversible (see Section Reproductive and Developmental Toxicity).

Refer to section 4.2 for Special Populations

4.7 Effects on ability to drive and use machines

Belumosudil has no influence on the ability to drive and use machines. The clinical status and adverse reactions experienced by the patient should be considered when assessing the patient's ability to perform tasks that require judgement, motor, or cognitive skills.

4.8 Undesirable effects

ADVERSE REACTIONS
The following CIOMS frequency rating is used, when applicable:

Very common ≥10 %; Common ≥ 1 and <10 %; Uncommon ≥ 0.1 and < 1%
Rare ≥ 0.01 and < 0.1 %; Very rare < 0.01 %, Unknown (cannot be estimated from available data).

CLINICAL TRIALS

Clinical Trial Study Data
In two open-label clinical trials (Study KD025-213 and Study KD025-208), 83 adult patients with chronic GvHD were treated with belumosudil 200 mg once daily (see Section Clinical Efficacy). As of 19 February 2020, the median follow-up time was 9.2 months, and the median duration of treatment was 6.9 months (range 0.5 to 38.7 months).

As of 19 February 2020, the most commonly occurring adverse reactions in the patients with chronic GvHD treated with 200 mg once daily belumosudil in clinical trials (≥ 20%) were fatigue, diarrhea, upper respiratory tract infection, nausea, dyspnea, cough, peripheral edema, and vomiting. The most common Grade 3 or 4 adverse reactions (≥ 5%) were pneumonia (7.2%), hyperglycemia (6.0%), and hypertension (6.0%).

The most frequent reasons for discontinuation were progression of chronic GvHD (13%) and recurrence of the underlying malignancy (8%) in patients with chronic GvHD treated with 200 mg once daily. Most common other adverse reactions leading to discontinuation were nausea (2.4%) and headache (2.4%). Adverse reactions leading to dose interruption occurred in 28.9% of patients were mainly infections (14.5%) including pneumonia (6.0%). Other adverse reactions (≥ 2%) leading to dose interruption were diarrhea (3.6%), hypotension (2.4%), vomiting (2.4%), and pyrexia (2.4%). The most commonly reported TEAEs (≥ 10% of belumosudil-treated subjects) are summarized by SOC and PT for subjects with chronic GvHD in Table 2.

Table 2 – Most Common (≥ 10%) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

Adverse Reaction	Belumosudil 200 mg once daily (N=83)	
	All Grades[a] (%)	Grade 3-4[a] (%)
Blood and lymphatic system disorders		
Anemia	12.0	4.8
Gastrointestinal disorders		
Diarrhea	32.5	3.6
Nausea	28.9	2.4
Vomiting	21.7	2.4
Dysphagia	15.7	0
Abdominal pain	12.0	1.2
General disorders and administration site conditions		
Fatigue	39.8	1.2
Edema peripheral	24.1	1.2
Pyrexia	16.9	1.2
Infections and infestations		
Upper respiratory tract infection	30.1	0
Pneumonia	10.8	7.2
Injury, poisoning and procedural complications		
Contusion	12.0	0
Investigations		
Alanine aminotransferase increased	12.0	1.2
Aspartate aminotransferase increased	12.0	1.2

Adverse Reaction	Belumosudil 200 mg once daily (N=83)	
	All Grades[a] (%)	Grade 3-4[a] (%)
Gamma-Glutamyl transferase increased	10.8	4.8
Metabolism and nutrition disorders		
Decreased appetite	14.5	1.2
Hyperglycemia	13.3	6.0
Musculoskeletal and connective tissue disorders		
Muscle spasm	15.7	0
Arthralgia	13.3	2.4
Nervous system disorders		
Headache	18.1	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea	26.5	3.6
Cough	24.1	0
Nasal congestion	12.0	0
Productive cough	10.8	0
Vascular disorders		
Hypertension	19.3	6.0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 and version 4.03.

Description of Selected Laboratory Abnormalities

Table 3 below displays shifts in Common Terminology Criteria (CTC) grade from baseline to maximum post-baseline for safety population, analysis group 1 in KD-025 Integrated Summary of Safety (ISS) for 83 patients in chronic GvHD studies (KD025-208 and KD025-213) who received belumosudil 200 mg once daily.

Table 3- Selected Laboratory Abnormalities Worsening from Baseline in Patients with cGvHD Who Received Belumosudil

	BELUMOSUDIL 200 mg once daily (N=83)		
	Grade 0-1 Baseline	**Grade 2-4 Max Post**	**Grade 3-4 Max Post**
Parameter	**N**	**%**	**%**
Chemistry			
Phosphate Decreased	76	28	7
Gamma Glutamyl Transferase Increased	47	21	11
Calcium Decreased	82	12	1
Alkaline Phosphatase Increased	80	9	0
Potassium Increased	82	7	1
Alanine Aminotransferase Increased	83	7	2
Creatinine Increased	83	4	0
Hematology			
Lymphocytes Decreased	62	29	13
Hemoglobin Decreased	79	11	1
Platelets Decreased	82	10	5
Neutrophil Count Decreased[a]	17	0	0
[a] Neutrophil data for KD025-208 study only.			

4.9 Overdose

There is no specific experience in the management of belumosudil overdose in patients. There is no known antidote for overdoses with belumosudil. Single doses up to 1000 mg have been given with acceptable tolerability in healthy volunteers. In the event of an overdose, undertake all appropriate supportive measures immediately.

5. Pharmacological properties

5.1 Mechanism of Action

Belumosudil is an inhibitor of Rho-associated, coiled-coil containing protein kinase (ROCK) which inhibits ROCK2 and ROCK1 with IC_{50} values of approximately 100 nM and 3 μM, respectively. Belumosudil down-regulated proinflammatory responses via regulation of STAT3/STAT5 phosphorylation and shifting Th17/Treg balance in ex-vivo or *in vitro*-human T cell assays. Belumosudil also inhibited aberrant pro-fibrotic signaling, *in vitro*. *In vivo*, belumosudil demonstrated activity in animal models of chronic GvHD.

5.2 Pharmacodynamic properties

Cardiac Electrophysiology
At a dose of 5 times the recommended dose, belumosudil does not prolong the QT interval to any clinically relevant extent.

5.3 Pharmacokinetic properties

The following pharmacokinetic parameters are presented for chronic GvHD patients administered belumosudil 200 mg once daily, unless otherwise specified. The mean (% coefficient of variation, %CV) steady-state AUC and C_{max} of belumosudil were 22,700 (48%) h*ng/mL and 2390 (44%) ng/mL, respectively. Belumosudil C_{max} and AUC increased in an approximately proportional manner over a dosage range of 200 and 400 mg (1 to 2 times once daily recommended dosage). The accumulation ratio of belumosudil was 1.35.

Absorption
Median T_{max} of belumosudil at steady state was 1.98 to 2.53 hours following administration of 200 mg once daily in patients. The mean (%CV) bioavailability was 63.7% (17.3%) following a single belumosudil dose in healthy subjects.

Effect of Food
In healthy subjects, the administration of a single 200 mg dose of belumosudil with a high-fat and high-calorie meal (800 to 1,000 calories with approximately 50% of total caloric content of the meal from fat) increased belumosudil C_{max} to 2.2 times that following fasted administration and AUC to 2 times that following fasted administration. Median T_{max} was delayed 0.5 hour.

Distribution
The geometric mean volume of distribution after a single dose of belumosudil in healthy subjects was 184 L (geo CV% 67.7%).

Belumosudil binding to human serum albumin and human α1-acid glycoprotein was 99.9% and 98.6%, respectively, *in vitro.*

Metabolism

Belumosudil is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C8, CYP2D6, and UGT1A9, *in vitro*.

Excretion

Following a single oral dose of radiolabeled belumosudil, in healthy subjects, 85% of radioactivity was recovered in feces (30% as unchanged) and less than 5% was recovered in urine.

Elimination

Belumosudil elimination half-life in patients (% coefficient of variation [CV]) was 19.0 h (39%).

Belumosudil clearance in patients (%CV) was 9.83 L/h (46%).

Special populations

Gender

Based on population PK analysis, there was no significant effects of sex on pharmacokinetics of belumosudil.

Race

Based on population PK analysis, there was no significant effects of race on pharmacokinetics of belumosudil.

Elderly

Age is not expected to affect the pharmacokinetics of belumosudil, based on clinical data.

Pediatric

Belumosudil pharmacokinetic have not been studied in pediatric population below 12 years of age.

Hepatic Impairment

In a single dose study, exposure to belumosudil increased by ≤ 1.5-fold in subjects with mild (Child- Pugh A) and moderate (Child-Pugh B) hepatic impairment. In subjects with severe hepatic impairment (Child-Pugh C), the AUC of belumosudil increased 4.21-fold while there was no apparent effect on its C_{max} (1.32-fold increase), relative to subjects with normal liver function.

Renal Impairment

Belumosudil pharmacokinetics are not affected by mild to moderate renal impairment. The effect of severe renal impairment on belumosudil pharmacokinetics has not been studied.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effects of Other Drugs on Belumosudil

Strong Cytochrome P450 (CYP) 3A Inhibitors: There was no clinically meaningful effect on belumosudil exposure when co-administered with itraconazole in healthy subjects.

Strong CYP3A4 Inducers: Coadministration of rifampin decreased belumosudil C_{max} by 59% and AUC by 72% in healthy subjects.

Moderate CYP3A Inducers: Coadministration of efavirenz is predicted to decrease belumosudil C_{max} by 19% and AUC by 35% in healthy subjects.

Proton Pump Inhibitors: Coadministration of rabeprazole decreased belumosudil C_{max} by 87% and AUC by 80%, and coadministration of omeprazole decreased belumosudil C_{max} by 68% and AUC by 47% in healthy subjects.

Effects of Belumosudil on Other Drugs

CYP3A Substrates: Coadministration of belumosudil is predicted to increase midazolam (a sensitive CYP3A substrate) C_{max} and AUC approximately 1.26- and 1.47-fold, respectively.

CYP2C9 Substrates: Coadministration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C9 substrates (such as warfarin).

CYP2C8 Substrates: Coadministration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C8 substrates that are not an OATP1B1 substrate.

Transporter systems

OATP1B1/BCRP substrates: Coadministration of belumosudil increases rosuvastatin Cmax and AUC by 3.6 and 4.6-fold, respectively (see Section Interactions).

P-glycoprotein (P-gp) substrates: Coadministration of belumosudil increased the exposure of dabigatran by 2-fold, indicating a moderate potential for inhibiting transport of P-gp substrates.

In Vitro Studies

Transporter Systems: Belumosudil is a substrate of P-glycoprotein (P-gp). Belumosudil inhibits BCRP, P-gp, and OATP1B1 at clinically relevant concentrations.

Enzymes Systems: Belumosudil is an inhibitor of CYP1A2, CYP2C19, CYP2D6, UGT1A1 and UGT1A9.

5.4 Clinical Efficacy

Chronic Graft versus Host Disease

Two open-label Phase 2 studies (studies KD025-213 and KD025-208) were conducted in patients with chronic GvHD. In both studies, the primary efficacy endpoint was the overall response rate (ORR), defined as the proportion of subjects who achieved a complete response (CR) or a partial response (PR) according to the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in chronic GvHD.

Study KD025-208 (N=54) was a dose-escalation, open-label, multicenter study of belumosudil for treatment of patients with chronic GvHD who had received 1 to 3 prior lines of systemic therapy and required additional therapy. Initiation of one or more new systemic therapies for chronic GvHD indicates a new line of therapy. Belumosudil was administered orally at 200 mg once daily (n=17), 200 mg twice daily (n=16), or 400 mg once daily (n=21). Concomitant treatment of chronic GvHD with corticosteroids and calcineurin inhibitors was permitted.

Study KD025-213 (N=132) was a randomized, open-label, multicenter study of belumosudil for treatment of patients with chronic GvHD who had received 2 to 5 prior lines of systemic therapy and required additional treatment. There were 66 patients treated with belumosudil 200 mg taken orally once daily, the other 66 patients received belumosudil 200 mg BID. Concomitant treatment with supportive care therapies for chronic GvHD was permitted. Concomitant treatment with GvHD prophylaxis and standard care systemic chronic GvHD therapies was permitted as long as the subject has been on a stable dose for at least 2 weeks prior to study. Initiation of new systemic chronic GvHD therapy while on study was not permitted.

Efficacy results are summarized in Table 4.

Table 4 - Best Overall Response Rate (ORR) and Other Efficacy Results in chronic GvHD Study

	KD025-213 (2-5 prior lines excluding subject 105-104) 200 mg once daily (N=65)
Overall Response Rate (%) [a]	49 (75%) [b]
95% CI	(63.1, 85.2)
K-M Duration of Response, Median, Weeks, 95% CI (Based on responder population)	1.9 (1.2, 2.9) [d]
≥7 Point Decrease in Lee Symptom Scale Score on Consecutive Assessments, n (%)	34 (52.3)

CI = Confidence Interval; K-M = Kaplan Meier; NR = Not Reached; KARA = Kadmon Algorithmic Response Assessment
a Responses assessed by investigators based on the 2014 NIH Response Criteria
b ORR is defined as the proportion of patients with best ORR of CR or PR through Cycle 7 Day 1
d This responder population is defined based on response status of KARA. Duration of response is defined as the time form first ORR response to progression of disease in any organ measure in comparison to nadir, new systemic therapy, or death, whichever comes first.

In study KD025-213, complete response (CR) was achieved in 4 patients along with partial response (PR) being achieved in majority of patients through Cycle 7 Day 1. The median time to response through Cycle 7 Day 1 was 1.8 weeks (range, 0.9 to 5.6 weeks). In patients who achieved response (N=49), no death or new systemic therapy initiation occurred in 65% (95% CI: 0.49, 0.77) of patients for at least 12 months since response.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Repeat Dose toxicity

Repeated oral dose studies with belumosudil of up 6-month in rats and 9-month in the dog were conducted. In the 6-month rat study, belumosudil was administered by oral gavage at 50, 125, and 275 mg/kg/day. The No-Observed-Adverse-Effect-Level (NOAEL) in the 6-month study was 275 mg/kg/day [male] /125 mg/kg/day [female] (~5- to 7-fold the AUC at the human recommended dose). In a 3-month dog study, gelatin capsules of belumosudil were administered orally at 35, 70, and 125 mg/kg/day with 4 weeks of recovery. In a separate 9-month study gelatin capsules of belumosudil were administered orally at 5, 20, and 40 mg/kg/day. The NOAELs in the 3-month and 9-month dog study were 35 mg/kg/day (~1-fold human AUC) and 40 mg/kg/day (~1-fold human AUC), respectively. Following administration of belumosudil to rats and/or dogs, the adverse effects observed in one or both species included toxicities in the gastrointestinal (GI) tract (emesis, loose stools, and/or abnormal black contents, increase in salivation), liver (elevated liver enzymes, hypertrophy/increased organ weight, and cholestasis/inflammation), kidney (increased blood urea nitrogen [BUN], tubular changes, pigmentation, intracellular protein droplets in the epithelium), hemolymphoid system (regenerative anemia), and reproductive system. The reproductive system toxicity involved both the male and female reproductive organs and associated tissues. In females, changes included lower uterine weights that correlated with uterine/cervical hypoplasia and decreased follicular development in rats at 275 mg/kg/day; findings were reversible. In males, toxicities included lower epididymis and testes weights associated with multifocal bilateral spermatozoan degeneration in the epididymis and testes, and multinucleated spermatids in

the testes, and the changes were reversible.

Genotoxicity

Belumosudil was not genotoxic in an *in vitro* bacterial mutagenicity (Ames) assay, *in vitro* chromosome aberration assay in human peripheral blood lymphocytes (HPBL) or an *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with belumosudil.

Reproductive and Developmental Toxicity

In a male and female rat fertility study, belumosudil-treated male animals were mated with untreated females, or untreated males were mated with belumosudil-treated females. Belumosudil was administered orally at doses of 50, 150 or 275 mg/kg/day to male rats 70 days prior to and throughout the mating period, and to female rats 14 days prior to mating and up to Gestation Day 7. At the dose of 275 mg/kg/day, adverse findings in female rats (treated with belumosudil or untreated but mated with treated males) included increased pre- or post-implantation loss and decreased number of viable embryos. Administration of belumosudil to male rats at a dose of 275 mg/kg/day resulted in abnormal sperm findings (reduced motility, reduced count, and increased percentage of abnormal sperm), and testes/epididymis organ changes (reduced weight and degeneration). Fertility was reduced in both treated males or females at the 275 mg/kg/day dose and reached statistical significance in males.

Adverse changes in male and female reproductive organs also occurred in general toxicology studies; findings included spermatozoa degeneration at a belumosudil dose of 35 mg/kg/day in dogs and decreased follicular development in ovaries at 275 mg/kg/day in rats. Changes were partially or fully reversed during the recovery period. The exposure (AUC) at the doses of 35 mg/kg/day in dogs, and 275 mg/kg/day in rats is 0.5 times and 8-9 times, respectively, the clinical exposure at the recommended dose of 200 mg daily.

Embryo-fetal development studies were conducted in rats with administration of belumosudil to pregnant animals during the period of organogenesis at oral doses of 25, 50, 150, and 300 mg/kg/day in a pilot study and doses of 15, 50, and 150 mg/kg/day in a pivotal study. In the pilot study, maternal toxicity and embryo-fetal developmental effects were observed. Maternal toxicity (reduced body weight gain) occurred at 150 and 300 mg/kg/day doses. Increased post-implantation loss occurred at 50 and 300 mg/kg/day. Fetal malformations were observed at ≥50 mg/kg/day and included absence of anus and tail, omphalocele, and dome shaped head. The exposure (AUC) at 50 mg/kg/day in rats is approximately 3 times the human exposure at the recommended dose of 200 mg.

In an embryo-fetal developmental study in rabbits, pregnant animals administered oral doses of belumosudil at 50, 125, and 225 mg/kg/day during the period of organogenesis resulted in maternal toxicity and embryo-fetal developmental effects. Maternal toxicity (body weight loss and mortality) was observed at doses ≥125 mg/kg/day. Embryo-fetal effects were observed at doses ≥50 mg/kg/day and included spontaneous abortion, increased post-implantation loss, decreased percentage of live fetuses, malformations, and decreased fetal body weight. Malformations included those in the tail (short), ribs (branched, fused or deformed), sternebrae (fused), and neural arches (fused, misaligned, and deformed). The exposure (AUC) at 50 mg/kg/day in rabbits is approximately 0.07 times the human exposure at the recommended dose of 200 mg.

Other Toxicity Studies

Phototoxicity

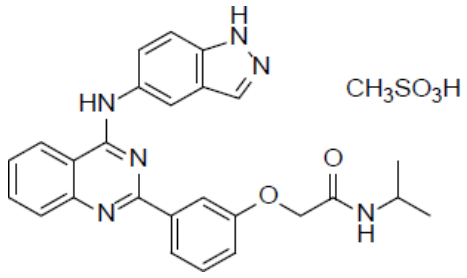
In-vitro belumosudil has demonstrated photo-absorbance between 290 and 370 nm and positive phototoxic

potential in the *in vitro* 3T3 Neutral Red Uptake Assay. No phototoxicity studies have been performed in animals. Based on standard reporting of adverse events in phase 1/2, belumosudil has not demonstrated any clinically significant ocular phototoxicity or skin related adverse events in patients.

7. Description

Active Moiety(Ies) / Active Ingredients

Belumosudil mesylate is a kinase inhibitor. The active pharmaceutical ingredient is belumosudil mesylate with the molecular formula $C_{27}H_{28}N_6O_5S$ and the molecular weight is 548.62 g/mol. The chemical name is 2-{3-[4-(1*H*-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide methanesulfonate (1:1). The chemical structure is as follows:



Belumosudil mesylate is a yellow crystalline solid. It is soluble in dimethylsulfoxide (DMSO), slightly soluble in dimethylformamide (DMF) and methanol, very slightly soluble in 2.0 pH (PBS buffer), and practically insoluble in water, acetonitrile, toluene, ethyl acetate, dichloromethane (DCM), acetone, isopropyl alcohol, n-heptane and in solutions at pH 2.0, 4.5, and 6.8 (PBS buffers).

Therapeutic or Pharmacological Class

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents.

ATC code: L04AA48 belumosudil

Pharmacological Class: Belumosudil is a Rho-associated, coiled-coil containing protein kinase-2 (ROCK2) selective kinase inhibitor.

8. Pharmaceutical particulars

8.1 Incompatibilities

No information

8.2 Shelf-life

Shelf Life: Refer outer carton.

8.3 Packaging information

200 mg tablets: 30 counts in 60 cc high-density polyethylene (HDPE) bottle with a desiccant.

8.4 Storage and handing instructions

Store at room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C and 30°C (59°F to 86°F).

Dispense to patient in original container only. Store in original container to protect from moisture. Replace cap securely each time after opening. Do not discard desiccant.

9. Patient Counselling Information

What is {product} used for?

Belumosudil is a prescription medicine used to treat adults and children 12 years of age and older with chronic graft-versus-host disease (chronic GvHD) after you have received at least 2 prior treatments (systemic therapy) and they did not work.

Do not use if:

- you are allergic (hypersensitive) to belumosudil or any of the other ingredients of this medicine.

Talk to your Doctor or pharmacist …

Before taking belumosudil, tell your healthcare provider about all your medical conditions, including if you:

- have kidney or liver problems
- are pregnant or plan to become pregnant
- are breastfeeding or plan to breastfeed

Other medicines and products

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Belumosudil may affect the way other medicines work, and other medicines may affect the way belumosudil works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Pregnancy and/or breastfeeding

If you are pregnant or plan to become pregnant, belumosudil can harm your unborn baby. If you are able to become pregnant, your healthcare provider will do a pregnancy test before starting treatment with belumosudil. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with belumosudil.

Females who can become pregnant should use effective birth control during treatment with belumosudil and for at least 1 week after the last dose.

Males with female partners who can become pregnant should use effective birth control during treatment with belumosudil and for at least 1 week after the last dose.

It is not known if belumosudil passes into breast milk. Do not breastfeed during treatment with belumosudil and for at least 1 week after the last dose.

Children and adolescents

Belumosudil should not be used in children under the age of 12 years. It is not known if belumosudil is safe and effective in children less than 12 years old.

Cautions on driving and using machinery

Be careful before you drive or use any machines or tools until you know how belumosudil affects you. Belumosudil is not expected to affect your ability to drive or operate machines.

How to use belumosudil

- Take belumosudil exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking belumosudil without first talking to your healthcare provider.
- Take belumosudil one time a day with a meal, unless instructed differently from your healthcare provider.
- Take belumosudil at about the same time each day.
- Swallow belumosudil tablets whole with a glass of water.
- Do not cut, crush, or chew belumosudil tablets.
- Your healthcare provider will do blood tests to check your liver at least 1 time a month during treatment with belumosudil.
- If you miss a dose of belumosudil, take it as soon as you remember on the same day. Take your next dose of belumosudil at your regular time on the next day. Do not take extra doses of belumosudil to make up for a missed dose.
- If you take too much belumosudil, call your healthcare provider or go to the nearest hospital emergency room right away.

Side effects

The most common side effects of belumosudil include:

- tiredness or weakness
- diarrhea
- infections
- nausea
- shortness of breath
- cough
- swelling
- high blood pressure
- headache
- muscle or bone pain
- stomach (abdominal) pain

Your healthcare provider may change your dose of belumosudil, temporarily stop, or permanently stop treatment with belumosudil if you have certain side effects.

These are not all the possible side effects of belumosudil.

Call your doctor for medical advice about side effects.

How to store belumosudil

Store belumosudil at room temperature between 68°F to 77°F (20°C to 25°C).

Keep belumosudil in its original container. The belumosudil bottle contains a desiccant packet to help keep your tablets dry (protect from moisture). Keep the desiccant in the bottle.

Tightly close the belumosudil bottle after you take your dose.

Keep belumosudil and all medicines out of the reach of children.

Ingredients/Composition

Active ingredient: belumosudil mesylate

Inactive ingredients:

– Tablet core: microcrystalline cellulose, hypromellose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

– Tablet coating: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide and yellow iron oxide.

10. Details of manufacturer

1. Manufacture, Packaging (primary and secondary), Labeling, Release testing, Stability testing
UPM PHARMACEUTICALS
501 Fifth Street
BRISTOL, TN 37620
United States

2. Labeling and Secondary Packaging of commercial batches
PHARMA PACKAGING SOLUTIONS, LLC dba Tjoapack, LLC
341 JD Yarnell Industrial Parkway
CLINTON, TN 37716
United States

11. Imported and Marketed by:
Sanofi Healthcare India Private Limited, Gala No. 4, Ground Floor, Building No. B1, Citylink Warehousing Complex, S No.121/10/A,121/10/B & 69, NH3, Vadape. Tal: Bhiwandi – 16 (Thane Z5) Pin: 421302

12. Details of permission or licence number with date

IMP-ND-49/2024 dated Nov 2024

13. Date of revision

Dec 2024
Ref : CCDS V2 dated 3rd Aug 2023